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PATENT COOPERATION TREATY

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INTERNATIONAL PRELIMINARY EXAMINATION REPORT

(PCT Article 36 and Rule 70)

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Applicant's or agent's file reference K 2839 Wd	**FOR FURTHER ACTION**	See Notification of Transmittal of International Preliminary Examination Report (Form PCT/IPEA/416)
International application No. PCT/DE00/02589	International filing date (*day month year*) 02 August 2000 (02.08.00)	Priority date (*day month year*) 06 August 1999 (06.08.99)
International Patent Classification (IPC) or national classification and IPC C12N 15/70		
Applicant DEUTSCHES KREBSFORSCHUNGSZENTRUM STIFTUNG DES ÖFFENTLICHEN RECHTS		

1. This international preliminary examination report has been prepared by this International Preliminary Examining Authority and is transmitted to the applicant according to Article 36.

2. This REPORT consists of a total of 8 sheets, including this cover sheet.

☐ This report is also accompanied by ANNEXES, i.e., sheets of the description, claims and/or drawings which have been amended and are the basis for this report and/or sheets containing rectifications made before this Authority (see Rule 70.16 and Section 607 of the Administrative Instructions under the PCT).

These annexes consist of a total of _____ sheets.

3. This report contains indications relating to the following items:

- I ☒ Basis of the report
- II ☐ Priority
- III ☒ Non-establishment of opinion with regard to novelty, inventive step and industrial applicability
- IV ☐ Lack of unity of invention
- V ☒ Reasoned statement under Article 35(2) with regard to novelty, inventive step or industrial applicability; citations and explanations supporting such statement
- VI ☐ Certain documents cited
- VII ☒ Certain defects in the international application
- VIII ☒ Certain observations on the international application

Date of submission of the demand 23 February 2001 (23.02.01)	Date of completion of this report 04 October 2001 (04.10.2001)
Name and mailing address of the IPEA/EP Facsimile No.	Authorized officer Telephone No.

INTERNATIONAL PRELIMINARY EXAMINATION REPORT

International application No.
PCT/DE00/02589

I. Basis of the report

1. With regard to the **elements** of the international application:*

☐ the international application as originally filed

☒ the description:
pages 1-10 . as originally filed
pages _____ . filed with the demand
pages _____ . filed with the letter of _____

☒ the claims:
pages 1-14 . as originally filed
pages _____ . as amended (together with any statement under Article 19
pages _____ . filed with the demand
pages _____ . filed with the letter of _____

☒ the drawings:
pages 2-4 . as originally filed
pages _____ . filed with the demand
pages 1 . filed with the letter of 18 December 2000 (18.12.2000)

☒ the sequence listing part of the description:
pages 1-8 . as originally filed
pages _____ . filed with the demand
pages _____ . filed with the letter of _____

2. With regard to the **language**, all the elements marked above were available or furnished to this Authority in the language in which the international application was filed, unless otherwise indicated under this item.
These elements were available or furnished to this Authority in the following language _____ which is:

☐ the language of a translation furnished for the purposes of international search (under Rule 23.1(b)).

☐ the language of publication of the international application (under Rule 48.3(b)).

☐ the language of the translation furnished for the purposes of international preliminary examination (under Rule 55.2 and/or 55.3).

3. With regard to any **nucleotide and/or amino acid sequence** disclosed in the international application, the international preliminary examination was carried out on the basis of the sequence listing:

☒ contained in the international application in written form.

☒ filed together with the international application in computer readable form.

☐ furnished subsequently to this Authority in written form.

☐ furnished subsequently to this Authority in computer readable form.

☐ The statement that the subsequently furnished written sequence listing does not go beyond the disclosure in the international application as filed has been furnished.

☐ The statement that the information recorded in computer readable form is identical to the written sequence listing has been furnished.

4. ☐ The amendments have resulted in the cancellation of:

☐ the description, pages _____

☐ the claims, Nos. _____

☐ the drawings, sheets/fig _____

5. ☐ This report has been established as if (some of) the amendments had not been made, since they have been considered to go beyond the disclosure as filed, as indicated in the Supplemental Box (Rule 70.2(c)).**

* *Replacement sheets which have been furnished to the receiving Office in response to an invitation under Article 14 are referred to in this report as "originally filed" and are not annexed to this report since they do not contain amendments (Rule 70.16 and 70.17).*

** *Any replacement sheet containing such amendments must be referred to under item 1 and annexed to this report.*

INTERNATIONAL PRELIMINARY EXAMINATION REPORT

International application No.
PCT/DE00/02589

III. Non-establishment of opinion with regard to novelty, inventive step and industrial applicability

1. The questions whether the claimed invention appears to be novel, to involve an inventive step (to be non obvious), or to be industrially applicable have not been examined in respect of:

☐ the entire international application.

☒ claims Nos. 12-14

because:

☒ the said international application, or the said claims Nos. 12-14 relate to the following subject matter which does not require an international preliminary examination *(specify)*:

☐ the description, claims or drawings *(indicate particular elements below)* or said claims Nos. _____ are so unclear that no meaningful opinion could be formed *(specify)*:

☐ the claims, or said claims Nos. _____ are so inadequately supported by the description that no meaningful opinion could be formed.

☐ no international search report has been established for said claims Nos. _____.

2. A meaningful international preliminary examination cannot be carried out due to the failure of the nucleotide and/or amino acid sequence listing to comply with the standard provided for in Annex C of the Administrative Instructions:

☐ the written form has not been furnished or does not comply with the standard.

☐ the computer readable form has not been furnished or does not comply with the standard.

Supplemental Box
(To be used when the space in any of the preceding boxes is not sufficient)

Continuation of: III

Claims 12 to 14 refer, insofar as they are used *in vivo*, to subject matter that is covered by PCT Rule 67.1(iv) in the opinion of the Examining Authority. Consequently, no opinion is established with respect to the industrial applicability of the subject matter of these claims (PCT Article 34(4)(a)(i)). See Box V, item 3.

V. **Reasoned statement under Article 35(2) with regard to novelty, inventive step or industrial applicability; citations and explanations supporting such statement**

1. Statement

Novelty (N)	Claims	1-14	YES
	Claims		NO
Inventive step (IS)	Claims		YES
	Claims	1-14	NO
Industrial applicability (IA)	Claims	1-11	YES
	Claims		NO

2. Citations and explanations

This report makes reference to the following documents:

D1 DE-C-43 37 197 (BIOTEST PHARMA GmbH), 25 August 1994;

D2 INTERNATIONAL JOURNAL OF CANCER, Vol. 77, no. 5, 31 August 1998, pages 763-772, (Kipriyanov S. et al.).

1. NOVELTY

The present application is novel as defined in PCT Article 33(2) because the available prior art does not disclose any constructs, expression vectors, transformants, methods, kits or uses with all of the features of the present claims.

2. INVENTIVE STEP

However, the present application does not meet the requirements of PCT Article 33(3).

2.1 D1, considered to be the closest prior art, discloses a bispecific antibody with binding sites for CD16 and CD30 (abstract; column 3, line 59 to column 4, line 11; Examples 6 to 8). The subject matter of present **Claim 1** differs from this prior

art only in that it is an Fv-antibody construct. Such Fv-constructs are easier to produce in large amounts and, moreover, cause fewer undesired immune reactions. The problem to be solved by the present invention can therefore be considered to be that of preparing alternative (and better) bispecific antibodies with binding sites for CD16 and CD30.

The solution proposed for this problem in **Claim 1** of the present application cannot be considered inventive (PCT Article 33(3)) because the production of bispecific Fv-antibody constructs is known to a person skilled in the art. With respect to bispecific Fv-antibody constructs (diabody) D2 describes the same advantages as the present application (abstract; page 763, right-hand column, lines 26 to 48; page 771, the last two paragraphs). A person skilled in the art would therefore consider it to be an obvious alternative to the bispecific antibody described in D1 to obtain an antibody with binding sites for CD16 and CD30. The subject matter of Claim 1 therefore does not involve an inventive step (PCT Article 33(3)).

Although CD16/CD30-Fv antibody construct has a quantitative larger level of cytotoxicity than the bispecific CD16/CD30 antibody from D1 (Example 3B and Figure 3 of the present application), the Examining Authority cannot agree with the applicant's argument (letter of 21.09.01) that this quantitative superiority may be surprising. However, a person skilled in the art knows from the prior art that Fv-antibody constructs can have a significantly higher level of cytotoxity as compared with bispecific antibodies (e.g. Figure 6 in D2) that can

be explained by a larger approximation of T-cells and the target cell (the column break on page 771 of D2). Moreover, since it is known (e.g. the last paragraph of D2) that Fv antibody constructs can be produced more economically than bispecific antibodies, a person skilled in the art would not have had only the ability but also a reason to replace bispecific antibodies by Fv-antibody constructs.

2.2 Dependent **Claims 2 to 6** appear to contain no features which, combined with the features of Claim 1, to which they refer, meet the PCT requirements concerning inventive step.

2.3 **Claims 7 to 10** refer to the construct of Claims 1 to 6 and cannot therefore be considered to be inventive (PCT Article 33(3)).

2.4 **Claim 11** relates to a kit with the construct of Claims 1 to 6 and/or the vector of Claims 7 to 8 (Box VIII, item 2). However, including non-inventive components in a kit would be straightforward for a person skilled in the art, especially since the resulting advantages are readily foreseeable. Consequently, the subject matter of Claim 11 does not involve an inventive step (PCT Article 33(3)).

2.5 The use of present **Claims 12 to 14** does not seem to involve an inventive step either, because D1 discloses the use of bispecific antibodies with binding sites for CD16 and CD30 for lysis of tumour cells from Hodgkin tumours (abstract, Claims 7 to 8).

3. INDUSTRIAL APPLICABILITY

The PCT Contracting States do not have uniform criteria for assessing the industrial applicability of **Claims 12 to 14** in their present form (insofar as they are used *in vivo*. Patentability may depend on the wording of the claims. The EPO, for example, does not recognise the industrial applicability of claims to the medical use of a compound; it does, however, allow claims to the first medical use of a known compound or to the use of such a compound in the manufacture of a drug for a new medical application.

4. P, X documents

The present application rightly claims the priority of an earlier application. Documents designated "P, X" in the international search report, which were published before the filing date of the present application, are therefore not relevant for the present application (PCT Rule 64.1(b)(ii)).

VII. Certain defects in the international application

The following defects in the form or contents of the international application have been noted:

Contrary to PCT Rule 5.1(a)(ii), the description does not cite D1 and D2 or indicate the relevant prior art disclosed therein.

VIII. Certain observations on the international application

The following observations on the clarity of the claims, description, and drawings or on the question whether the claims are fully supported by the description, are made:

1. The expression "Fv-antibody construct" used in the claims is not clear as defined in PCT Article 6 because this expression does not clearly show that said construct does not designate any constant domains (as defined in the present description, page 2, lines 19 to 23).

2. The German words "erfindungsgemässes [according to the invention]" or "erfindungsgemässen [according to the invention]" used in **Claim 11** are not clear (PCT Article 6) because the technical features of the constructs and vectors respectively do not follow clearly from them. Consequently, Claim 11 should refer to "an Fv-antibody construct according to any one of Claims 1 to 6" or "an expression vector according to any one of Claims 7 to 8".